A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 9/30/10 has been entered.

Claims 1-26 have been canceled and claims 27-35 are still at issue and are present for examination.

Applicants' arguments filed on 9/30/10, have been fully considered but are not deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation

under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 27-31 and 33-35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Olsen et al. (WO 00/64482) in view of either of Yick et al. (reference C1 of applicants IDS of 7/07) or Zuo et al. (reference CAG of applicants IDS of 4/06)

Olsen et al. teach a chimeric protein composed of two portions a first component capable of suppressing or neutralizing a neurite growth inhibitory molecule and a second component capable of stimulating neurite growth and/or regeneration. (see page 4) and pharmaceutical compositions thereof. Olsen et al. specifically teach that the component capable of stimulating neurite growth and/or regeneration can be a neurotrophic molecule including NGF, BDNF, NT3, FGF and many others (see page 10). Olsen et al. further teach that the neurite growth inhibitory molecule which is inhibited or suppressed by the first component of the chimeric molecule includes chondroitin proteoglycans (see page 25). Olsen et al. further teach that the two components of the chimeric molecule may be optionally separated by a peptide linker (see page 8). Olsen et al. do not explicitly teach that the component capable of suppressing or neutralizing a neurite growth inhibitory

molecule is a polypeptide possessing matrix modification activity or particularly a chondroitinase such as chondroitinase ABC.

Each of Yick et al. and Zuo et al. teach that chondroitin proteoglycans are extracellular matrix components which inhibit neuronal growth and regeneration following injury and that the administration of chondroitinase ABC which degrades chondroitin proteoglycans promotes axonal regeneration.

Therefore, it would have been obvious to one of ordinary skill in the art to select chondroitinase ABC as the component capable of suppressing or neutralizing a neurite growth inhibitory molecule in the chimeric molecule of Olsen et al. as the disclosures of Yick et al. and Zuo et al. show that chondroitinase ABC has all the properties that are preferred in this component as disclosed by Olsen et al. Furthermore, claims 34 and 35 are included in the rejection as pharmaceutical compositions of the chimeric proteins would have been obvious to one of ordinary skill in the art and determining the optimum therapeutic dose of a desired pharmaceutical composition is well within the ordinary skill in the art.

Applicants argue that substituting the prior art amphibody's first component with chondroitinases, hyaluronidases, or matrix metalloproteinases would destroy the

intended purpose of the Olson amphibody. Applicants argue that the amphibody of Olsen has three requisite features (sequestration of a growth inhibiting region, change of this inhibitory region into a growth promoting one and a directed pattern of nerve growth), all of which would be destroyed by the instant rejection. However, this is simply not true and contrary to applicants assertion all of these features would be expected to be present in the chimeric protein as suggested in the rejection. As previously noted enzymes do in fact bind their substrates and thus the enzyme of the claimed chimeric protein will in fact also function to localize the chimeric protein (including the attached growth promoting portion thereof to the site of the enzymes substrate (i.e., sequestration to the inhibitory region), and clearly degradation of the inhibitory molecules themselves in conjunction with the fact that the other portion of the chimeric protein is a growth promoting protein will change the inhibitory region into a growth promoting region as the inhibitory substrate is gone and the chimeric protein is located in the position where the inhibitory region previously was. Furthermore the directed pattern of nerve growth (versus a random pattern) is a direct result of the localization of the growth stimulatory protein of the amphibody of Olsen to the growth inhibitory region. Since one would expect the chimeric

protein suggested in the rejection to have this effect also one would clearly expect it to also provide for a directed pattern of nerve growth.

Applicants argue that it is a requisite disclosure of Olson that the "anti-" end of the amphibody must bind to inhibitory molecules in the tissue environment and thereby sequester these regions. However, as noted the suggested chimeric protein of the rejection will do just this as enzymes also bind specifically to their substrates, just as antibodies bind to their antigens. The only difference between the two is that antibodies do not degrade their antigens while the suggested enzymes will do so. However, to the extent the word "sequester" is used to mean "remove or isolate from", clearly degradation of the growth inhibitory region would be encompassed within the term "sequester" as it would be completely removed and it is not clear what other meaning the term "sequester" (as used in the context of the disclosure of Olsen) could be given. Furthermore as was previously stated, applicants characterization of Olsen is narrow and not inclusive of all that Olsen teaches. The "anti-end" of the chimeric protein of Olsen is not restricted to antibodies and is not taught to solely have the function of localization and binding. This end of the chimeric protein disclosed by Olsen et al. is specifically disclosed as including

inhibitors/suppressors of proteoglycans (see page 22) and in particular chondroitin proteoglycans (page 25) and is explicitly disclosed as having the function of "suppressing or neutralizing a neurite growth inhibitory effect" (see page 4). Clearly degradation will neutralize.

Applicants argue that the next fundamental aspect of Olson is that once the inhibitory region is sequestered with the Olson "amphibody," that the former inhibitory region is then converted into a growth-promoting region and an antibody moiety or a moiety with specific binding such as with antibodies is needed under Olson to achieve this conversion function. However, none of this excludes enzymes as suggested in the rejection. Enzymes bind specifically to their substrates just like antibodies bind specifically to their antigens. Furthermore, it would be expected that a chimeric protein as suggested in the rejection would be more effective than an antibody at converting the growth inhibitory region to a growth promoting region as the enzyme will actually degrade the growth inhibitory compounds (leaving only the chimeric protein including its growth promoting portion while the antibodies will simply bind the growth inhibitory compounds and thereby prevent their interaction with the regenerating nerves or other factors.

Applicants argue that the chimeric protein suggested in the rejection would also destroy the third requisite feature of Olsen, namely directed rather than random nerve growth regeneration. However, this is not true as the chimeric protein suggested by the rejection would be expected to produce this feature as well. This feature is produced by the first to features, i.e., localization of the chimeric molecule to the site of the growth inhibitory compounds and conversion of this site to a growth promoting region. These same features, would be expected in the chimeric molecule suggested in the rejection as it will bind to its substrate and thereby localize its growth promoting end to the region that the substrate was present. Although degradation of the substrate will then allow further movement of the chimeric protein, the process would be expected to simply repeat itself. Thus in fact a skilled artisan would believe that this might result in the need to use less of a chimeric protein as suggested than a chimeric protein comprising an antibody as a single chimeric protein as suggested could convert several different growth inhibitory sites to growth promoting sites while one comprising an antibody would remain anchored at a single site indefinitely. Applicants argue that Olsen teaches away from turning the inhibitory site into a merely neutral site and emphasizes turning the site into a

stimulatory site. However, the suggested chimeric protein would NOT turn the inhibitory site into a merely neutral site but would as Olsen's amphibody turn it into a growth promoting site. The suggested chimeric protein also includes a growth promoting end identical to that of the amphibody of Olsen which when the suggested protein binds to the enzyme substrate (i.e. the growth inhibitory substance) will be localized to this region and thus upon the degradation of the substrate will be a growth promoting region due to the presence of the growth promoting portion of the suggested chimeric molecule which will remain at the site.

Applicants state that the examiner argued that Olson does not teach or suggest that keeping the structure of the inhibitory molecule intact is important but if the inhibitory molecule were to be degraded, the amphibody could not dock and cap, and provide a "chemoattractant railway.". However, this is not persuasive as the degradation of the substrate will only occur after the substrate is bound by the chimeric protein and the function of localizing the "pro-end" to the correct site has been accomplished.

Applicants argue that the art (Dou et al.) teaches that the degradation products of proteoglycans also have "quantitatively identical" growth inhibitory effects and thus one would not be motivated to use the degradation enzymes as the "anti" end.

However, this argument in fact ignores the disclosures of Yick and Zuo (both published after the disclosure of Dou et al.) who experimentally showed that degradation of chondrotin sulfate by chondroitinase ABC actually promoted axonal regeneration. If the products of the degradation were equally inhibitory to the substrate no such promotion would be expected.

Claim 32 is rejected under 35 U.S.C. 103(a) as being unpatentable over Olsen et al. (WO 00/64482) in view of either of Yick et al. or Zuo et al. as applied to claims 27-31 and 33-35 above, and further in view of Gearing (US Patent 5,262,522).

Olsen et al., Yick et al. and Zuo et al. are discussed above but do not explicitly disclose the use of an immunoglobulin Fc portion as the peptide linker between the two portions of the chimeric protein.

Gearing et al. teach a chimeric protein having two separate polypeptide domains optionally separated by a peptide linker. Gearing et al. teach that a preferred peptide linker is an immunoglobulin Fc portion (see column 8, lines 17-43).

Therefore, it would have been obvious to one of ordinary skill in the art to select an immunoglobulin Fc portion as the peptide linker of the chimeric molecule of Olson et al. as Gearing et al. specifically teach this as a preferred linker

molecule for another chimeric protein formed by the conjugation of two proteins which don't naturally occur together.

Applicants traversal of the instant rejection is merely a recapitulation of the traversal of the rejection above, which has already been addressed in detail, and a listing of what is missing from each reference individually. However, the rejection was made under 35 U.S.C. 103(a) thus explicitly acknowledging that each reference alone does not teach all of the limitations of the and applicants present no argument as to why one would not combine them as suggested.

All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS

of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Rebecca E. Prouty whose telephone number is 571-272-0937. The examiner can normally be reached on Tuesday-Friday from 8 AM to 5 PM. The examiner can also be reached on alternate Mondays

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Robert Mondesi, can be reached at (571) 272-0956. The fax phone number for this Group is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Rebecca Prouty/
Primary Examiner
Art Unit 1652